PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61L 12/14 | A1

(11) International Publication Number: WO 00/07634

(43) International Publication Date: 17 February 2000 (17.02.00)

(21) International Application Number: PCT/US99/17853

(22) International Filing Date: 5 August 1999 (05.08.99)

(30) Priority Data:
09/130,542 6 August 1998 (06.08.98) US

(71) Applicant: NDT, INC. [US/US]; Suite O–290, 30100 Town Center Drive, Laguna Nigel, CA 92677 (US).

(72) Inventors: DE BRUIJN, Chris; Gartenstiege 25, D–48683 Ahaus (DE). CHRIST, F., Richard; 650 Lombardy Lane, Laguna Beach, CA 92651 (US). DZIABO, Anthony, J.; 21241 Avenida Nubes, Lake Forest, CA 92630 (US). VIGH, Joseph; 500 Fordham Drive, Placentia, CA 92670 (US).

(74) Agents: KIRCHANSKI, Stefan, J. et al.; Graham & James LLP, 14th Floor, 801 S. Figueroa Street, Los Angeles, CA 90017–5554 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CONTACT LENS AND OPHTHALMIC SOLUTIONS

(57) Abstract

Benzyldimethyl{2–[2–(p–1,1,3,3–tetramethylbutylphenoxy)ethoxy]ethyl} ammonium chloride (BDT) forms the basis of contact lens solutions that are unusually effective at reducing the number and wide variety of pathogenic microorganisms that may infect rigid gas permeable or soft contact lenses. Furthermore, it has been discovered that natural occurring compounds alone and in combination with chemical agents can be used in ophthalmic solutions such as contact lens solution to enhance and complement their anti–microbial, cleaning and wetting activity or to reduce irritation to the eye. The basic contact lens solution comprises an effective concentration of BDT (preferably 1 to 100 parts per million), with naturally occurring plant products possessing activities complementary to BDT, in an isotonic diluent buffered with a physiologically acceptable buffer to a physiologically natural range.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Contact Lens and Ophthalmic Solutions

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to contact lens and ophthalmic solutions and in particular relates to methods to disinfect and clean soft and rigid gas permeable (RGP) contact lenses, effectively and safely while maintaining convenience and comfort for the contact lens wearer.

By "effectively" we mean that the levels of specified pathogenic micro-organisms as well as other contaminants such as proteins, lipids, etc., are removed or reduced by a prescribed amount within the period of time contact lenses are kept in their storage case and storage solution. This is commonly taken to be "overnight" which is estimated as 6 hours. By "safely" we mean that the prescribed reduction in pathogen and other contaminant levels is accomplished without concomitant damage to the tissues of the human eye and without deleterious alteration of the contact lens itself. By "convenience" we mean that the contact lens care solution will be such that a minimum number of steps will be required to render the contact lenses clean and disinfected and the complete compliance of the wearer to the prescribed contact lens care procedures will be more likely. By "comfort" we mean that the eyes of the wearer will be able to tolerate the direct instillation of the solution.

DESCRIPTION OF RELATED ART

Currently available contact lenses are made of hydrogels causing them to be soft so that they can be comfortably worn. Previously, contact lenses were either hard plastic (PMMA) or RGP and required the contact lens wearing patient to adjust to the uncomfortable sensation of a foreign body in the eye. The advent of soft contact

lenses has resulted in an increased adoption of contact lenses by the general population.

Contact lenses are commonly worn on a daily basis and kept in a storage case/solution during the night hours or whenever they are not being worn. During the wear and normal handling of contact lenses, microorganisms as well as biomolecules such as lipids, proteins, etc. can become adhered to the contact lenses and thus transferred to the storage case/solution. Furthermore, a tear film that contains proteins, lipids, and even microorganisms, which represent the natural flora of the ocular surface, covers the surface of the eye. Any of these components found in the tear film or on the external surface of the eye or the surrounding skin can be carried into the storage case/solution on the contact lens.

Some of the microorganisms that may be transferred from the eye or fingers to the storage case/solution may multiply therein and may later be pathogenic to the human cornea or other ocular structures. When the contact lens is returned to the eye following its overnight soaking period, it is possible for these pathogens to be applied to the surface of the eye. Although human tears contain natural anti-microbial agents, a pathogen-bearing lens in contact with the cornea of the eye can serve as a reservoir of infection that might overcome the eye's natural defenses. This is especially the case for soft contact lens as the material tends to uptake the microorganisms. The result of microbial growth—bacterial, protozoan or even fungal—can cause damage to the eye resulting in impaired vision and even blindness. Therefore, contact lenses should be daily disinfected to eliminate pathogenic organisms, usually overnight, i.e., six to eight hours, to protect the wearer's eyes from infection.

As has been stated earlier, it is also possible that other materials of biological origin can be transferred to the contact lens during wear and upon handling and transfer between the eye and the storage case/solution. These materials include

cellular debris, proteins, lipids, and inorganic ions such as those of calcium and magnesium. Such materials can adsorb to the surface or become embed in the sub-surface matrix of the soft contact lens often creating persistent deposits that can cause irritation by abrasion against ocular tissues, e.g., cornea and inner surfaces of the eye lids. Furthermore, these deposits can become sufficiently severe to significantly reduce the transparency of the contact lens perhaps leading to impairment of the optical performance of the contact lens. It is therefore of interest to prevent the deposition of or to break up any aggregations of these contaminating molecules during the period of overnight immersion of the contact lenses in the storage case/solution.

Various solutions have been developed over the years to ensure that contact lenses are essentially pathogen and deposit free and can be safely and comfortably worn following overnight storage. These contact lens solutions typically include anti-microbial substances as well as cleaning (active against both lipids and proteins), wetting and other agents for the disinfection and cleaning of contact lenses during storage after wear. These solutions generally have sufficient microbicidal activity that the numbers of potentially pathogenic microorganisms are reduced to a prescribed level during the overnight soaking period.

Disinfection agents typically used for other applications such as hard surface disinfection, instrument disinfection, topical skin disinfection, etc. are not necessarily applicable to contact lens and ophthalmic solutions. The high concentration used and aggressive nature of many of these agents are unsuitable for use with contact lenses due to interaction or damage to the lens or irritation to ocular tissue. "Strong" disinfecting agents are compounds such as thimerasol, chlorhexidine, hydrogen peroxide, and benzalkonium chloride. For example, three (3%) percent hydrogen peroxide instilled directly in the eye or a lens soaked in hydrogen peroxide and applied to the eye will result in pain and severe irritation.

In the case of hydrogen peroxide, prior art answers to the problem of irritation are disclosed in U.S. Patents 3,912,451, 4,585,488, 5,145,644 and 5,7666,931. These references show various methods and chemistries wherein the disinfecting period is followed by a neutralizing step using catalase, an enzyme that catalyzes the breakdown of hydrogen peroxide to water. This approach has found some level of acceptance among contact lens wearers. However, acceptance has remained limited, because of the multiple steps of disinfection, neutralization, and rinsing are not convenient to the wearer. More importantly, the potential exists for the neutralization and rinsing steps to be completed incorrectly (non-compliance) leading to the potential for some residual hydrogen peroxide to come in contact with the surface of the eye with the onset of severe stinging and irritation.

More recently, so-called multipurpose solutions (MPS) with chemical disinfection agents, as disclosed in U.S. Patents 4,407,791, 4,525,346, 4,758,595, 4,820,352, 4,836,956, 5,422,073, 5,560,186, 5,593,637, and 5,756,045, have largely supplanted hydrogen peroxide systems in the marketplace because they are far more convenient than the hydrogen peroxide systems. In this case the wearer need only purchase and use a single solution leading to advantages in cost and convenience. The challenge of disinfection and cleaning without harm to the eye or the lens is particularly acute with the MPS products, however, since all of the various activities, e.g., wetting, contaminant dispersion, and disinfection, are required to co-exist in a single solution without antagonistic effects of one component on the activity of another. Furthermore, because the MPS can be instilled directly into the eye, the active anti-microbial component of these solutions must provide the required degree of pathogen reduction while being free of irritating or damaging sequelae to the surface and the anterior segment of the eye or to the contact lens itself. There is no

opportunity with an MPS to neutralize or rinse away the anti-microbial agent prior to applying the contact lens to the eye.

Generally therefore the art has found it difficult to formulate these MPS solutions to satisfy the following performance criteria. The successful solution must:

1. Show anti-microbial activity to reduce the numbers of common pathogens found on contact lenses to prescribed levels;

2. Show an ability to retard the deposition processes of proteins, lipids, and other materials onto or into the lens and to remove such deposits if they have formed;

3. Be nonirritating to the eye without the help of rinsing and/or neutralizing solutions;

4. Be free of toxic metals or compounds and sensitizing agents so that no long term allergic or toxic response is provoked;

5. Not adversely accumulate within or on the lens or adversely alter the wettability or the parameters (i.e., size, shape, and optical properties) of the lens or be released in amounts toxic to the eye during lens wear;

6. Show adequate shelf-life (e.g. chemical stability);

7. Compatible with enzymes and other agents used in artificial tears or similar accessories to contact lens wear.

A prior art alternative to the use of chemical disinfecting agents are phenolic compounds (e.g., bioflavonoids) as disclosed in De Bruijn International Application

PCT/NL97/00092 and Dutch patent NL-1002484. Natural plant derived substances; such as bioflavonoids, can be employed in contact lens care products as natural disinfecting or preserving agents. While the use of bioflavonoids is desirable because they are natural plant products, the majority of bioflavonoids are complex combinations that are difficult to obtain, reproduce and assay.

As background, the method for evaluating the effectiveness of a disinfectant generally requires measuring the ability of the agent to reduce the numbers of viable organisms during a period of time consistent with the normal period of storage of contact lenses between wearings such as six to eight hours, i.e., "overnight". This reduction of numbers of organisms is typically reported in terms of the change in the common log of the microbial population as a result of exposure to the anti-microbial agent. For example, if the agent has effected a reduction in the concentration of a particular organisms in a challenge solution from 10^6 colony forming units (cfu) per milliliter (ml) to 10^2 cfu/ml within six hours of exposure then the change, or "log reduction", of the organism as a result of exposure to the agent would be 4.0 (logs). In other words, the number of viable organisms have been reduced to one ten-thousandth of the original level.

In procedures for verifying the effectiveness of contact lens disinfectants generally recognized guidelines call for the use of *Candida albicans* (a yeast), *Fusarium solani* (a mold), *Pseudomonas aeruginosa* (a Gram-negative bacterium), *Staphylococcus aureus* (a Gram-positive bacerium), *and Serratia marcescens* (a Gram-negative bacterium). It is generally accepted in the field of ophthalmic and contact lens solutions

that an effective disinfectant will cause at least a three log reduction of each of the bacterial species and a one log reduction of each of the yeast and mold within the storage time advocated for the contact lens care system, typically six to eight hours, i.e., "overnight".

These tests are most often performed by challenging the solution with a concentrated inoculum (e.g., 10^5-10^6 cfu/ml) of each test organism. Over time samples are taken and plated on a growth medium to estimate the number of live organisms remaining at each time point. Of particular interest is the six-hour time point that represents the duration of typical overnight storage of soft contact lenses. It should be apparent that such a challenge represents a worst case scenario since a far greater number of microbes is added than would ever be expected on a contact lens. Further, it should also be apparent that the results of the test may be significantly influenced by other components of the solution besides the disinfectant agent.

In the case of contact lens and ophthalmic solutions various agents are added to enhance compatibility with the eye. To avoid stinging or irritation it is important that the solution possess a tonicity and pH within the physiological range, e.g., 200-350 mOsmole for tonicity and 6.5-8.5 for pH. To this end, various buffering and osmotic agents are often added. The simplest osmotic agent is sodium chloride since this is a major solute in human tears. In addition propylene glycol, lactulose, trehalose, sorbitol, mannitol or other osmotic agents may also be added to replace some or all of the sodium chloride. Also, various buffer systems such as citrate, phosphate (appropriate mixtures of Na_2HPO_4, NaH_2PO_4, and KH_2PO_4), borate (boric acid, sodium borate, potassium

tetraborate, potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5.

Various viscosity building agents such as polyethylene glycol, surfactants, polyvinylpyrrolidone, polyvinyl alcohol, carboxymethyl cellulose and similar materials may be added to adjust the "body" and "feel" of the solution. Surface active agents, such as polysorbates, polyoxyethylenes and certain phosphonates may be added to ensure proper wetting and/or cleaning. Sequestering agents such as ethylenediaminetetraacetic acid (EDTA), phosphonates, citrate, gluconate and tartarate are also common additives for preservatives of, disinfection or cleaning solutions.

To date, the significant challenge in the development of ophthalmic and contact lens solutions, particularly the MPS solutions, has been to find disinfection agents with sufficient anti-microbial activity that are not at the same time damaging to the eye or contact lens. Due to the complex requirements to keep soft, hydrogel contact lenses clean, free of pathogen microbes, and comfortable to wear without damaging or changing the lens polymer or dimensional parameters and without any harm or side effects to the human eye, only very few compounds or systems have been qualified as suitable ophthalmic or contact lens solutions. It is therefore the object of the present invention to provide a solution that combines the use of a chemical agent (BDT) and natural ingredients with the strength of harsh chemical agents such as hydrogen peroxide while avoiding irritation or damage to the eye.

SUMMARY OF THE INVENTION

The present invention concerns the unexpected discovery that the disinfectant compound, BDT (**B**enzyl**D**imethyl-[2-[2-[(p-1,1,3,3 **T**etramethyl butyl) phenoxy)ethoxy]ethyl] ammonium chloride), which has been widely tested and used in hospital surface disinfection, topical pharmaceutical preparations, and even as preservatives for injectables has unexpectedly proven highly effective in the disinfection of contact lenses without irritation to the external ocular surfaces or alteration of the parameters of the contact lens itself. Further, it has been discovered that BDT is stable in aqueous solution and can coexist in an formulation with the variety of cleaning, tonicity, and comfort additives common to ophthalmic and contact lens solutions without an adverse effect on its activity. Finally, it has also been discovered that the effectiveness of ophthalmic solutions containing BDT can be successfully enhanced by the addition of naturally occurring plant products.

The basic active ingredient formulation of the present invention comprises an effective concentration of BDT (preferably 1 to 100 parts per million), either alone or with other additives, in an isotonic or nearly isotonic diluent buffered with an acceptable buffer to the physiologically natural range.

It has been discovered that a variety of discrete, isolated and well-characterized natural plant compounds show anti-microbial and cleaning activity. It has also been discovered that some of these anti-microbial compounds act in a synergistic and or complementary manner with other anti-microbial compounds, such as BDT, and thus enhances their anti-microbial action. The potential range of these anti-microbial compounds includes glycosides, alkaloids, phenolics (anthocyanins,

quinones, flavonols and flavonoids, etc.), and terpenoids (including phytosterols and carotenoids). Of particular interest are the following anti-microbial compounds; Allicin, Aucubin, Berberine, Bilberry extract, Caffeic Acid, Chlorogenic Acid, Echinacea extract, Ferulic Acid, Hydrastine, Lipoic Acid, Naringin, Oleuropein, Proanthocyanidins, Quercetin, and Rutin as stand alone disinfection agents or in combination with other anti-microbial agents.

Further, it has been discovered that saponins, can be used as a natural plant surface active or cleaning agents in lens solutions. Specifically triterpenoid saponins and steriod saponins are particularly effective in contact lens or ophthalmic solutions. Also, a wide range of other comfort and cleaning enhancers can be added to the basic solution without adverse affects on the activity of these natural compounds or combinations. Suitable additives include, but are not limited to, various wetting, buffering, osmotic, sequestering, and comfort enhancing agents can be added to enhance the final formulation. .

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following description is provided to enable any person skilled in the art to make and use the invention and sets forth the best modes contemplated by the inventors of carrying out their invention. Various modifications, however, will remain readily apparent to those skilled in the art, since the general principles of the present invention have been defined herein, specifically to provide an improved contact lens care solution.

The following examples will be employed to demonstrate the effectiveness of BDT as well as its compatibility and being complementary with other desirable additives. In progressing through these examples one can understand the “building blocks” of the preferred embodiment of contact lens and ophthalmic solutions incorporating BDT.

Example 1

Initial tests of BDT were made in a contact lens disinfectant solution containing a sodium phosphate buffer system (0.1% anhydrous monobasic sodium phosphate and 0.4% anhydrous dibasic sodium phosphate) made isotonic with sodium chloride (0.7%) and also including Pluronic F127 (0.2%), a polyoxyethylene. Various concentrations of BDT in these vehicles were tested for anti-microbial activity against three of the five organisms that make up the commonly accepted disinfection test panel. The "log reduction" data at six hours after challenge are shown in Table 1. "Log reduction" is the format of data presentation in all of the examples that follow. From these and additional similar experiments it has been observed that increasing concentration of BDT results in increasing kill of a wide range of microbes in six hours or less.

Table 1: Effect of BDT Concentration on Microbial Kill

	15 ppm BDT	25 ppm BDT
S. aureus	1.7	>5.0
P. aeruginosa	1.8	3.4
C. albicans	0.3	1.4

Example 2

Experiments with a variety of different buffering agents discovered interactions between BDT and the buffer. In particular , a borate-based formula (0.3% boric acid, 0.4% sodium borate, 0.4% sodium chloride and 0.2% Pluronic F127) produced a wider spectrum of microorganism kill than the comparable phosphate-based solution. Especially noteworthy is the enhanced kill of fungus (*Candida albicans*) effected by the use of the borate buffer.

Table 2: Comparison of Anti-microbial Activity of BDT in Borate vs. Phosphate Buffer

	25 ppm BDT Borate	25 ppm BDT Phosphate
S. aureus	>5.0	>5.0
P. aeruginosa	>5.0	3.4
C. albicans	4.3	1.4

Example 3

A wide variety of naturally occurring compounds shows anti-microbial activity. In Table 3a results are shown for the enhancement of the kill of *Pseudomonas aeruginosa* using Chlorogenic Acid and Berberine in a phosphate buffered solution with 25 ppm BDT.

Table 3a: Enhancement of *Pseudomonas* kill with Chlorogenic Acid or Berberine

	25 ppm BDT	25 ppm BDT 500 ppm Chlorogenic Acid	25 ppm BDT 100 ppm Berberine
P. aeruginosa	3.4	4.5	>5.0

In Table 3b Caffeic Acid, combined with BDT in the presence of borate buffer, 250 ppm Chlorogenic Acid, and 0.2% Glycerin, improves the kill of *Pseudomonas aeruginosa* while maintaining the excellent log reductions for *Staphylococcus aureus* and *Candida albicans.*

Table 3b: Anti-microbial Enhancement of Caffeic Acid to BDT/Chlorogenic Acid

	25 ppm BDT/250 ppm Chlorogenic Acid	25 ppm BDT/250 ppm Chlorogenic Acid/ 1000 ppm Caffeic Acid
P. aeruginosa	2.8	>5.0
S. aureus	>5.0	>5.0
C. albicans	>5.0	3.8

Example 4

Table 4 shows the effect of adding 0.2% Glycerin to 25 ppm BDT and 250 ppm chlorogenic acid with borate buffer. In terms of microbiological disinfection this solution is very effective. The addition of Glycerin, a naturally occurring compound has essentially no effect on the disinfectant properties. There is evidence that Glycerin can reduce any minor toxic effects that a disinfectant agent might have on mammalian cells.

Table 4: Effect of the Addition of Glycerin on Anti-Microbial Activity

	25 ppm BDT 250 ppm Chlorogenic Acid 0.2% Glycerin	25 ppm BDT 250 ppm Chlorogenic Acid
S. aureus	>5.0	>5.0
P. aeruginosa	3.9	4.4
C. albicans	3.8	4.0

Example 5

Table 5 shows the effect of adding 0.2% Decanedioic Acid and 0.2% Glycerin to a formulation consisting of 25 ppm BDT and 1000 ppm Caffeic Acid in Borate Buffer. Decanedioic Acid is believed to improve the ocular comfort of contact lens

solutions. As show in Table 5, there is no negative impact on anti-microbial activity with both Glycerin and Decanedioic Acid.

Table 5: Effect of the Addition of Glycerin + Decanedioic Acid on Anti-Microbial Activity

	25 ppm BDT 1000 ppm Caffeic Acid	**25 ppm BDT 1000 ppm Caffeic Acid 0.2% Glycerin 0.2% Decanedioic Acid**
S. aureus	>5.0	>5.0
P. aeruginosa	>5.0	>5.0
C. albicans	3.3	>5.0

Example 6

When the solutions were tested on animals, there was no observed toxicity or irritation when the materials were used in a "normal wear" cycle. That is, an isotonic BDT solution at physiological pH was tested on rabbits using Wohlk Weflex lenses. The lenses were disinfected in the test solution or in a control solution overnight. The lenses were then applied to the animals and worn by the animals for 8 hours of every 24 hours. This cycle was repeated for 21 days with no signs of irritation or toxicity. A second study used SUREVUE™ contact lenses. The lenses were soaked in the test solutions for 12 hours and then applied to the eyes of animals for a 12 hour wear cycle. Then a freshly soaked lens was substituted. This exaggerated wear test was on for 14 days of continuous wear of the test period. At the end examination of the animal eyes showed no signs of irritation or toxicity. Equivalent results were noted for the control solution, which was a commercially marketed MPS.

Example 7

A clinical study was conducted over a three month period with seven patients wearing SUREVUE™ (*n*=6) and Medalist™ (*n*=1) contact lenses. Patients received new lenses at the beginning of the study. The lenses were soaked overnight in an

isotonic BDT test solution at physiological pH and rinsed in saline prior to wear. After 21 days there were no significant slit lamp findings, no irritation of the conjunctiva and no lens deposits reported. No irritation or other negative findings were found during the tenure of the study.

Example 8

Table 8-a shows the anti-microbial activity of two naturally-occurring compounds, caffeic acid and chlorogenic acid, at 1000 ppm in borate-buffered saline. The borate-buffered saline alone was used as a control. It is evident that both naturally-occurring compounds have substantial anti-microbial activity against *Pseudomonas aeruginosa* within the six-hour challenge period. Either compound therefore may be useful as a preservative or disinfectant agent in a ophthalmic solutions.

Table 8-a: Anti-Microbial Activity of Caffeic Acid and Chlorogenic Acid in Borate-Buffered Saline

	Borate-Buffered Saline	**1000 ppm Caffeic Acid**	**1000 ppm Chlorogenic Acid**
S. aureus	0	0.7	0.4
P. aeruginosa	0	>5.0	2.2
C. albicans	0	0.2	0.1

Table 8-b shows the anti-microbial activity of a third naturally-occurring compound, berberine, at concentrations of 25 and 100 ppm in phosphate-buffered saline. It is evident that 100 ppm berberine has anti-microbial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* within the 6-hour challenge period. Berberine may therefore be useful as a preservative or disinfectant agent in a ophthalmic solutions.

Table 8-b: Anti-Microbial Activity of Berberine at Two Concentrations in Phosphate-Buffered Saline

	25 ppm Berberine	100 ppm Berberine
S. aureus	0	1.5
P. aeruginosa	0.1	1.8
C. albicans	0	0

Many alterations and modifications may be made by those having ordinary skill in the art without departing from the scope of the present invention. The words used in this specification to describe the invention and its various embodiments are to be understood not only in the sense of their commonly defined meanings, but to include by special definition in this specification structure, material or acts beyond the scope of the commonly defined meanings. Thus if an element can be understood in the context of this specification as including more than one meaning, then its use in a claim must be understood as being generic to all possible meanings supported by the specification and by the word itself.

CLAIMS

We claim:

1. A contact lens solution containing a microbicidal concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride.

2. The contact lens solution of Claim 1, wherein the concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride is between 1 and 100 parts per million.

3. The contact lens solution of Claim 1, further comprising a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

4. The contact lens solution of Claim 1, further comprising a osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, andpropylene glycol.

5. The contact lens solution of Claim 1, further comprising between 0.01% and 5.0% glycerin.

6. The contact lens solution of Claim 1 further comprising between 0.01% and 2.0% of decanedioic acid.

7. The contact lens solutions of Claim 1 further comprising between 10 and 2500 parts per million of allantoin.

8. The contact lens solution of Claim 1 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, and saponins.

9. The contact lens solution of Claim 1 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

10. The contact lens solution of Claim 1 further comprising a naturally-occurring compound as an additional microbicidal agent and selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

11. The contact lens solution of Claim 1 further comprising a viscosity altering agent.

12. The contact lens solution of Claim 11, wherein the viscosity altering agent is selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, cellulose polymers and mixtures thereof.

13. An ophthalmic solution comprised of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

14. The ophthalmic solution of Claim 13 further comprising a viscosity altering agent.

15. The ophthalmic solution of Claim 13 further comprising a sequestering agent.

16. The ophthalmic solution of Claim 13 further comprising a wetting agent.

17. The ophthalmic solution of Claim 13 further comprising an osmotic agent.

18. The ophthalmic solution of Claim 16, wherein the wetting agent comprising a saponin.

19. A contact lens solution comprising: between 1 and 100 parts per million Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride, between 10 and 10000 parts per million of a naturally-occurring plant product, and borate buffer.

20. The contact lens solution of Claim 19 further comprising an osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, and propylene glycol.

21. The contact lens solution of Claim 19 further comprising between .01% and 2.0% glycerin.

22. The contact lens solution of Claim 19 further comprising between 0.01% and 2.0% of decanedioic acid.

23. The contact lens solutions of Claim 19 further comprising between 10 and 2500 parts per million of allantoin.

24. The contact lens solution of Claim 19 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, and saponins.

25. The contact lens solution of Claim 19 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

26. The contact lens solution of Claim 19 wherein the naturally-occurring plant product is selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

27. The contact lens solution of Claim 19 further comprising a viscosity altering agent.

28. The contact lens solution of Claim 27, wherein the viscosity altering agent is selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, and cellulose polymer.

29. A contact lens solution comprising: between 10 and 50 parts per million Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride, between 100 and 2000 parts per million of caffeic acid and a borate buffer.

30. The contact lens solution of Claim 29 further comprising an osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, and propylene glycol.

31. The contact lens solution of Claim 29 further comprising between .01% and 2.0% glycerin.

32. The contact lens solution of Claim 29 further comprising between 0.01% and 2.0% of decanedioic acid.

33. The contact lens solutions of Claim 29 further comprising between 10 and 2500 parts per million of allantoin.

34. The contact lens solution of Claim 29 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and mixtures thereof;

35. The contact lens solution of Claim 29 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

36. The contact lens solution of Claim 29 further comprising a viscosity altering agent selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, and cellulose polymers.

37. An ophthalmic solution comprising between 0.01% and 2.5% saponins as a wetting agent.

38. An ophthalmic solution comprising a naturally-occurring microbicidal compound selected from the group consisting of berberine, caffeic acid, and chlorogenic acid, and a borate buffer.

39. A method for cleaning and disinfecting contact lenses comprising the steps of:

contacting a contact lens to be cleaned and disinfected with an aqueous solution of between 1 and 100 parts per million of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride;

leaving the lens in contact with said aqueous solution for a predetermined time; and

removing the lens from said solution and placing it onto a user's eye without rinsing.

40. The method of Claim 39, wherein said aqueous solution further comprises a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

41. The method of Claim 39, wherein said aqueous solution further comprises a naturally-occurring plant product as an additional microbicidal agent and selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

42. The method of Claim 39 wherein the contact lens is selected from the group consisting of rigid gas permeable contact lenses and soft contact lenses.

43. A method for cleaning and disinfecting contact lenses comprising the steps of:

contacting a contact lens to be cleaned and disinfected with an aqueous solution of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin;

leaving the lens in contact with said aqueous solution for a predetermined time; and

removing the lens from said solution and placing it onto a user's eye without rinsing.

44. The method of Claim 43, wherein said aqueous solution further comprises a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

44. The method of Claim 43, wherein said aqueous solution further comprises between wherein the concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride is between 1 and 100 parts per million.

45. The method of Claim 43 wherein the contact lens is selected from the group consisting of rigid gas permeable contact lenses and soft contact lenses.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/17853

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L12/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C11D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

	Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
13	X	WO 96 06603 A (ALCON LAB INC) 7 March 1996 (1996-03-07) example 7 claims 1,3-5,7-10	1-4,9
13	X	WO 92 21049 A (ALLERGAN INC) 26 November 1992 (1992-11-26) page 6, line 6 claims 1,3	13-16, 43,44
13	X	WO 94 00160 A (ALLERGAN INC) 6 January 1994 (1994-01-06) claims	13-16, 43,44

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 1999	21. 12. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thornton, S

2

International Application No
PCT/US 99/17853

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

	Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1	X	WO 97 41215 A (HENRIKSEN LOTTE RUGHOLM ;LYKKE MADS (DK); NOVONORDISK AS (DK)) 6 November 1997 (1997-11-06) page 13, line 15 - line 17 page 22, line 17 ---	13-17,38
1	X	US 3 943 251 A (MEDOW NORMAN B ET AL) 9 March 1976 (1976-03-09) the whole document ---	13,14,38
1	X	US 5 691 379 A (ELSTNER ERICH FRANZ ET AL) 25 November 1997 (1997-11-25) column 7, line 13 - line 15 column 11, line 41 - line 48 claims ---	13-16
1	X	EP 0 812 592 A (KIKKOMAN CORP) 17 December 1997 (1997-12-17) page 5, line 55 - line 56 claims ---	13
1	X	US 5 591 773 A (GRUNBERGER DEZIDER ET AL) 7 January 1997 (1997-01-07) claims ---	13
1	X	FR 2 426 698 A (ROSENBERG EDY) 21 December 1979 (1979-12-21) the whole document ---	13
1	X	US 5 182 258 A (CHIOU GEORGE C Y) 26 January 1993 (1993-01-26) claims 1,2,6 ---	37
13	P,X	WO 99 23887 A (NOVONORDISK AS) 20 May 1999 (1999-05-20) claims 1-7,12 -----	13

2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/17853

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See further information sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-12,19-36,39-42

   A contact lens solution containing BDT

2. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal allicin

3. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal aucubin

4. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal berberine

5. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal bilberry extract

6. Claims: 13-36,38,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of the following naturally occurring microbiocidal 3,4-hydroxycinnamic acid (caffeic acid) derivatives: caffeic acid, chlorogenic acid, echinacea extract, and ferulic acid

7. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal hydrastine

8. Claims: 13-28,43-45

   An ophthalmic solution comprised of between 10 and 10000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

parts per million of naturally occurring microbiocidal lipoic acid

9. Claims: 13-28,43-45

An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal naringin

10. Claims: 13-28,43-45

An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal oleuropein

11. Claims: 13-28,43-45

An ophthalmic solution comprised of between 10 and 10000 parts per million of naturally occurring microbiocidal proanthocyanidins

12. Claims: 13-28,43-45

An ophthalmic solution comprised of between 10 and 10000 parts per million of a naturally occurring microbiocidal selected from quercin, rutin

13. Claim : 37

An ophthalmic solution comprising between 0.01% and 2.5% saponins as a wetting agent

The problem underlying the application is, according to the description, a method to disinfect and clean contact lenses by reducing levels of microorganisms and proteins, etc. by using a compound in an ophthalmic solution.

Each of the above inventions is presented as a separate solution to the problem underlying the application. For the application to meet the requirements of unity of invention (Rule 13.1) the above inventions must be so linked as to form a single general inventive concept, i.e. there must be a technical relationship among the inventions involving one or more of the same or corresponding special technical features (Rule 13.2).
The technical features common to each of the inventions are ophthalmic solutions which contain compounds which can reduce levels of microorganisms and proteins.

Documents US3943251 (column 1, line 50-54), US5591773 (see

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

abstract), WO9221049 (page 6, line 6, claim 1, 3), etc. disclose these features as solutions to the same problem. So, it is apparent from the cited state of the art that the technical features common to the various inventions defined above are not novel and therefore cannot be considered as special technical features within the meaning of Rule 13.2. Since the single general concept is not novel, it cannot be the single general inventive concept which is required to be present by Rule 13.1 PCT, and hence, there is lack of unity.

In the present application no further technical features can be distinguished that are shared by all inventions and, could be regarded as "special technical features" established in the technical relationship among the different inventions.

The application is divided according to the different claimed embodiments, which differ substantially and represent mere alternative solutions to the problem underlying the application.
The different inventions have been grouped according to structural similarites, e.g. caffeic acid/chlorogenic acid/echinacea extracts/ferulic acid and quercin/rutin are structurally related (source: Merck Index). In this way, the application has been divided into 13 (grouped) inventions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/17853

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9606603	A	07-03-1996	AU	3155195	A	22-03-1996
WO 9221049	A	26-11-1992	AU	656385	B	02-02-1995
			AU	1894892	A	30-12-1992
			CA	2109205	A	11-11-1992
			EP	0583367	A	23-02-1994
			JP	6507503	T	25-08-1994
			NZ	242358	A	25-03-1994
			PT	100471	A	29-10-1993
WO 9400160	A	06-01-1994	AT	180680	T	15-06-1999
			AU	674862	B	16-01-1997
			AU	4542193	A	24-01-1994
			CA	2138960	A	06-01-1994
			DE	69325174	D	08-07-1999
			EP	0648131	A	19-04-1995
			ES	2132241	T	16-08-1999
			JP	7508523	T	21-09-1995
			US	5387394	A	07-02-1995
WO 9741215	A	06-11-1997	AU	2635097	A	19-11-1997
			EP	0896618	A	17-02-1999
US 3943251	A	09-03-1976	US	3903282	A	02-09-1975
US 5691379	A	25-11-1997	AU	6566794	A	20-12-1994
			CA	2162467	A	08-12-1994
			DE	4345199	A	01-12-1994
			WO	9427592	A	08-12-1994
			EP	0697863	A	28-02-1996
			JP	8511246	T	26-11-1996
			ZA	9403514	A	02-02-1995
EP 0812592	A	17-12-1997	JP	10059846	A	03-03-1998
			US	5804597	A	08-09-1998
US 5591773	A	07-01-1997	AU	2122995	A	03-10-1995
			WO	9524899	A	21-09-1995
FR 2426698	A	21-12-1979	NONE			
US 5182258	A	26-01-1993	US	5283236	A	01-02-1994
			US	5278142	A	11-01-1994
WO 9923887	A	20-05-1999	AU	9737998	A	31-05-1999